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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,619	01/09/2002	Li Chen	1122	6985

151 7590 06/02/2003

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EXAMINER	
BERNHARDT, EMILY B	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 06/02/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/042,619	Applicant(s) CHEN et al.
	Examiner Emily Bernhardt	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-64* is/are pending in the application.

4a) Of the above, claim(s) *17-24, 27, 28, 47-52, and 61-63* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-16, 25, 26, 29-46, 53-60, and 64* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-16,25-26,29-47,53-60 and 64, drawn to piperazine compounds of formula (I) where R3/R4 do not further form rings,compositions and use and intermediates thereof (claim 64), classified in class 544, subclass 121, 364,367; class 514 subclass 254.02,etc.

II. Claims 1-7, 17-24,25-28,30-31,33,41,45,47,53,56-60, drawn to compounds of formula (I) where R3/R4 further fuse to form up two additional rings, compositions and use thereof, classified in class 544, subclass 367 and other subclasses as determined by the exact nature of ring system(s) formed; class 514 subclass 254.02,etc.

III. Claims 50-52 and 63, drawn to polymer-bound compounds, classified in class 521, subclasses 25, 30.

IV. Claims 48,49 and 61, drawn to piperazine derivatives, classified in class 544, subclass 395.

V. Claim 62, drawn to ethanone derivatives, classified in class 568, subclass 308.

The inventions are distinct, each from the other because of the following reasons: Compounds of I and II are drawn to dissimilar compounds that are not art-recognized equivalents of each other and are separately classified when the rings contain hetero atoms such as one or more N atoms alone or combined with other atoms - all generically embraced. Different issues of patentability may arise. The groups are made and used independently and can support separate patents.

Inventions I/II and III-V are related as mutually exclusive species in an intermediate-final product relationship. Distinctness is proven for claims in this relationship if the intermediate product is useful to make other than the final product (MPEP § 806.04(b), 3rd paragraph), and the species are patentably distinct (MPEP § 806.04(h)). In the instant case, the intermediate product is deemed to be useful as precursors to other products distinct from that claimed herein such as piperidines and other azines or have industrial/pharmaceutical applications themselves and the inventions are deemed patentably distinct since there is nothing on this record to show them to be obvious variants. Should applicant traverse on

the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions anticipated by the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Ms. Rocha-Tramaloni on 5/12/03 a provisional election was made with right of traverse to prosecute the invention of I, claims 1-16,25,26,29-47,53-60 and 64. Affirmation of this election must be made by applicant in replying to this Office action. Claims 17-24,27,28,48-52 and 63 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims linking groups I and II will only be examined with respect to the elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be

accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

The abstract of the disclosure is objected to because the structure of final products is not depicted. Correction is required. See MPEP § 608.01(b).

The disclosure is objected to because of the following informalities: Mention of U.S. provisional applications for which benefit under 119(e) is being sought need to be inserted in the specification on p.1. See MPEP 1302.04.

Appropriate correction is required.

Claims 1-16,25,26,30,31,33,37-41,43,45,53-60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1.Recitation of a pharmaceutically acceptable .... ester" is of unclear scope. While specification defines some groups for esterification of COOH groups (see p.12), when present in the compounds, there is no guidance as to what other sites can be esterified and with what types of esters? Many different compounds can result from the derivitization to such different types of esters and specification provides no guidelines as to what constitutes any one suitable ester other than for COOH

groups. Such limitation cannot be read into the claims. Note In re Priest 199 USPQ 11.

2.Resultant rings formed at NR7R8, N12N13,NR15R16 are not clearly defined in the claims nor in the specification . What are the other atoms in the ring and how are they situated with respect to the the mandatory "N" atom? Adjacent, non-adjacent? Are they saturated, unsaturated? Note In re Wiggins 179 USPQ 421 regarding such terminology. The only guidance seen is on p.18 where 3 specific rings are described for NR12R13 as R4.

3. In claim 16 the variable being defined is not set forth. It may be that R4 was intended.

4.Claims 38-40 recite species outside the scope of claim 37. Note that claim 37 requires that **each of** R3-R5 be selected from the 3 groups recited in the claim resulting in trisubstituted phenyl species.

5. In independent claim 53 R5 is not defined.

6. The proviso appearing in main claim 1 on p.147 and elsewhere in the claims requires some clarification. It appears its purpose is to exclude m-NO_2, p-Cl phenyl

compounds. If that is the case note that R5 also at the meta position can be NO_2 as well and thus would not exclude the intended compounds. Clarification is needed.

Claims 1-16, 25-26,30-31,33,37,41,43,45,53,56-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

1. Specification is not adequately enabling for the scope of NR7R8, NR12R13 and NR15R16 forming rings which read on an assortment of rings both saturated and unsaturated with hetero atoms in any array. Only 3 rings have been particularly identified and this only for NR12R13. There is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Such diverse and all encompassing embodiments would not all be expected to show the same activity such as the instantly disclosed uses- for treating cancer, which is a very structure sensitive art. See In re Fouche 169 USPQ 429: In re Surrey 151

USPQ 724 regarding sufficiency of disclosure for Markush groups and see In re Fisher 166 USPQ 18 regarding requirements for enablement in cases directed to physiological activities.

2. Scope of method claim directed to treating all cancers is not enabled. Cancers in general are difficult to treat and applicants provide no competent evidence that instantly disclosed assay tests are reasonably predictive of in vivo efficacy for any one cancer much less any and all embraced in the method claims 58-60. Note Grant, a very recent publication, while discussing CDK inhibitors as effective in blocking neoplasms in preclinical testing does not evidence that CDK inhibitors are a known class of broad-based anti-tumor agents for treating man. In fact the article stresses the research in this area is in the preliminary stages of development. See p.18 left column and p.20 section 4. Where the utility is unusual or difficult to treat or speculative, the examiner has authority to require evidence that tests relied on are reasonably predictive of in vivo efficacy by those skilled in the art. See for example, In re Ruskin 148 USPQ 221; Ex parte Jovanovics 211 USPQ 907. Also, note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a),August 2000 edition. Thus given the level of skill in this art which is

low and the lack of direction (i.e. art-recognized tests) provided as to what might be treatable and in what dosage compounds are to be administered, as well as the lack of direction (i.e. working examples) provided as to what other rings as NR7R8, N12R13,NR15R16 might work this rejection is being applied.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16,25,26,29-36,38,41-46,53-60 and 64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chong (WO'845). The WO publication provided by applicants discloses very similar compounds to that claimed herein for treating cancers based on inhibition at one or more CDK kinases the same activity relied on herein. See compounds such as C71, C81, C96, C97, C100, C105, C111, C121, H2, H3, J1-J3 appearing on pages 59-117 which differ only in placement of substituents on phenyl -i.e. at ortho position and additionally at meta and para. While instant claims do not cover ortho substitution, Chong teaches substitution at all ring positions as described on p.10 and includes many of the substituents permitted

herein (halo,alkyl,alkoxy,CN, alkylthio,amino) and otherwise has the same type of substituents on piperazino nitrogen (R1) as claimed herein. See p.9. Thus the relationship that exists among these compounds and instant compounds is that of position isomerism. Compounds that are position isomers are expected to have similar properties. See for example In re Crounse 150 USPQ 554; Ex parte Engelhardt 208 USPQ 343; In re Mehta 146 USPQ 284; In re Norris 84 USPQ 458 and MPEP 2144.09 (2/03 Edition) regarding position isomerism. Thus it would have been obvious to one skilled in the art at the time the invention was made to expect instant compounds to be also potentially useful as CDK inhibitors in view of the close structural similarity outlined above.

Applicants' IDS filed 3/12/02 has been considered only in part as references C1 and C2 are not seen in the file. Also note that ref. B11 is a duplicate cite of B1. The supplemental "IDS" filed 7/8/02 is only a copy of applicants' EP Search Report. There is no disclosure statement as indicated on the cover page.

Was the proviso in the claims excluding NO2 and Cl on phenyl necessitated by prior art? If so applicants are requested to identify such. The examiner has not found any art describing such compounds.

Any inquiry concerning this communication should be directed to Emily Bernhardt at telephone number (703) 308-4714.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

E Bernhardt

EMILY BERNHARDT

PRIMARY EXAMINER

GROUP 1600